Guidelines on

Male Sexual Dysfunction:

Erectile dysfunction and premature ejaculation

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1. BACKGROUND

1.1 Introduction

Erectile dysfunction (ED) and premature ejaculation (PE) are the two main complaints in male sexual medicine (1,2). New oral therapies have completely changed the diagnostic and therapeutic approach to ED and the Guidelines Office of the European Association of Urology (EAU) has appointed an Expert Panel to update previously published EAU guidelines for ED or impotence.

1.2 Methodology

For Chapters 2 and 3 (Erectile Dysfunction and Treatment of Erectile Dysfunction) a systemic literature search performed by the panel members. The MedLine database was searched using the major Medical Subject Headings (MeSH) terms “erectile dysfunction”, “sexual dysfunction” “ejaculation”. All articles published between January 2009 (previous update) and January 2013 were considered for review. For Chapter 4 (Premature Ejaculation) the MedLine search was supplemented by the term “premature ejaculation” in all search fields, for this 2014 print, covering a time frame up to August 2013. The Expert Panel has also identified critical problems and knowledge gaps, setting priorities for future clinical research.

1.3 Level of evidence and grade of recommendation

References in the text have been assessed according to their level of scientific evidence (LE), and guideline recommendations have been graded follow the listings in Tables 1 and 2, based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (3). Grading aims to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

**Modified from (3).*

It should be noted that when recommendations are graded, the link between the LE and grade of recommendation (GR) is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level of evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as “upgraded based on panel consensus”. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a grade is assigned (4-6).

The EAU Guidelines Office does not perform structured cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever these data are available, the expert panel will include the information.

Table 2: Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

**Modified from (3).*

1.4 Publication History

The first European Association of Urology (EAU) Guidelines on Erectile Dysfunction were published in 2000 (6) with subsequent updates in 2001, 2002, 2004, 2005, 2009, 2013 and 2014. In particular the 2009 document presented a significant update of the previous publication with the inclusion of the topic “Premature Ejaculation” and the text was renamed to “EAU Guidelines on Male Sexual Dysfunction" (7). In 2011 the expert panel decided to develop separate guidelines addressing Penile Curvature, which resulted in a separate publication in 2012 (8). Recently a guideline on Priapism was completed (9).

Several scientific summaries have been published in the EAU scientific journal, European Urology (10-14). Quick reference documents (pocket guidelines) are available presenting the main findings of both the Male Sexual Dysfunction Guidelines and the Penile Curvature Guidelines. These documents follow the updating cycle of the underlying large texts. All material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of translations and republications produced by national urological associations: http://www.uroweb.org/guidelines/online-guidelines/.

1.5 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

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2. ERECTILE DYSFUNCTION

2.1 Epidemiology and risk factors

Erection is a neuro-vasculo-tissular phenomenon under hormonal control. It includes arterial dilatation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism (1,2).

Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Although ED is a benign disorder, it may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners (3). There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease; thus, ED should not be regarded only as a QoL issue but also as a potential warning sign of cardiovascular disease (4-8).

*2.1.1 **Epidemiology***

Epidemiological data have shown a high prevalence and incidence of ED worldwide. The first large, community-based study of ED was the Massachusetts Male Aging Study (MMAS) (3). The study reported an overall prevalence of 52% ED in non-institutionalised men aged 40-70 years in the Boston area; specific prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% (9). In the National Health and Social Life Survey (NHSLS), the prevalence of sexual dysfunction in males (not specific ED) was 31% (10). The incidence rate of ED (new cases per 1,000 men annually) was 26 in the MMAS study (11), 65.6 (mean follow-up of 2 years) in a Brazilian study (12), and 19.2 (mean follow-up of 4.2 years) in a Dutch study (13). In Taiwan, the prevalence of ED was 27% among all patients investigated and 29% among those aged ≥ 40 years (14). In Ghana, the overall prevalence of ED was 59.6% and there were positive correlations between ED, dissatisfaction, age and other sexual dysfunctions (15). Differences between these studies can be explained by differences in methodology and in the ages, socioeconomic and cultural status of the populations studied.

Data from epidemiological studies have demonstrated consistent and compelling evidence for an association between lower urinary tract symptoms (LUTS)/benign prostatic hypertrophy (BPH) and sexual dysfunction in aging men that is independent of the effects of age, other comorbidities, and various lifestyle factors (16). The Massachusetts Male Aging (MSAM-7) study systematically investigated the relationship between LUTS and sexual dysfunction in > 12,000 men aged 50-80 years. It was performed in the US and six European countries (France, Germany, Italy, Netherlands, Spain, and UK). Eighty-three percent of men considered themselves sexually active, and 71% reported at least one episode of sexual activity in the past 4 weeks. The overall prevalence of LUTS was 90%. Only 19% of men had sought medical help for LUTS and only 11% were medically treated. The overall prevalence of ED was 49%, and 10% of patients reported complete absence of erection. The overall prevalence of ejaculation disorders was 46% and 5% reported anejaculation (17).

*2.1.2 **Risk factors***

Erectile dysfunction shares common risk factors with cardiovascular disease (e.g., lack of exercise, obesity, smoking, hypercholesterolaemia, and metabolic syndrome); some of which can be modified. Moreover, men with mild ED have similar risk factors to those of a general ED clinical trial population. Thus, mild ED is an important indicator of risk for associated underlying disease. Men complaining of mild ED should be evaluated adequately (for underlying cardiovascular risk) (18).

In the MMAS, men who began exercising in midlife had a 70% reduced risk for ED compared to sedentary men and a significantly lower incidence over an 8-year follow-up period of regular exercise (19). A multicentre, randomised, open-label study in obese men with moderate ED compared 2 years of intensive exercise and weight loss with a control group given general information about healthy food choices and exercise (20). Significant improvements in body mass index (BMI) and physical activity scores, as well as erectile function, were observed in the lifestyle intervention group. These changes were highly correlated with both weight loss and activity levels.

Some studies have shown some evidence that lifestyle modification and pharmacotherapy for cardiovascular risk factors are effective in improving sexual function in men with ED. However, it should be

emphasized that more controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED (6).

*2.1.3 **Post-radical prostatectomy ED, post-radiotherapy ED & post-brachytherapy ED***

Radical prostatectomy (RP) in any form (open, laparoscopic, or robotic) is a widely performed procedure for patients with clinically localised prostate cancer and a life expectancy of at least 10 years. This procedure may lead to treatment-specific sequelae affecting health-related QoL. This outcome has become increasingly important with the more frequent diagnosis of prostate cancer in younger patients (21-22). Research has shown that 25-75% of men experience postoperative ED (23). A systematic review has shown that incidence of potency recovery after robotic prostatectomy is influenced by numerous factors. It reported, for the first time, a significant advantage in favor of robotic laparoscopic radical prostatectomy in comparison with retropubic radical prostatectomy in terms of 12-month potency rates (24). However, there was no significant difference between laparoscopic RP and robot-assisted laparoscopic RP. Currently, we do not have enough evidence-based data to confirm that robot-assisted laparoscopic RP has any advantageous effect on functional outcome. Experience of the surgeon seems to be the main factor besides preservation of neurovascular bundles and patient age.

Post-RP ED is multifactorial. Cavernosal nerve injury induces proapoptotic (loss of smooth muscle) and profibrotic (increase in collagen) factors within the corpora cavernosa. These changes may also be caused by poor oxygenation due to changes in the blood supply to the cavernosa because of possible arterial damage during the surgical procedure.

Preoperative potency is a major factor associated with the recovery of erectile function after surgery, therefore, patients being considered for nerve-sparing radical prostatectomy (NSRP) should ideally be potent preoperatively (24-29). It is also clear that cavernosal nerves must be preserved to ensure erectile function recovers after RP. In addition, the role of vascular insufficiency is of increasing interest in postoperative ED (30,31).

ED is also a common sequela after external beam radiotherapy and brachytherapy for prostate cancer. The mechanisms contributing to ED after prostate irradiation involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue (32,33). Alternative treatments for prostate cancer including cryotherapy and high-intensity focused ultrasound are associated with equivalent or worsened rates of ED compared to surgery or radiation therapy (34,35).

*2.1.4 **Managing ED: implications for everyday clinical practice***

Advances in basic and clinical research in ED during the past 15 years have led to the development of a variety of new treatment options, including pharmacological agents for intracavernous, intraurethral, and oral use (36-38). Reconstructive vascular surgery is reserved for select cases of arterial insufficiency, with no current indications for venous ligation procedures, given the poor overall outcomes (39,40).

An increasing number of men are currently seeking help for ED due to the growing public awareness of the condition and the availability of effective, safe and user-friendly oral drug therapy. However, not all physicians evaluating and treating ED have appropriate background knowledge and clinical experience in sexual medicine. Thus, men with ED may receive little or no evaluation before treatment and will therefore not receive treatment for any underlying disease that may be causing their ED. Other men without ED may be requesting treatment simply to enhance their sexual performance.

*2.1.5 **Conclusions on the epidemiology of ED***

	LE
Erection is a neuro-vasculo-tissular phenomenon under hormonal control.	2b
ED is common worldwide.	2b
ED shares risk factors with cardiovascular disease.	2b
Lifestyle modification (intensive exercise and decrease in BMI) can improve erectile function.	1b
ED is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
ED is common after radical prostatectomy, irrespective of the surgical technique used.	2b
ED is common after external radiotherapy and brachytherapy.	2b

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2.2 Diagnostic evaluation

2.2.1 ***Basic work-up***

The first step in evaluating ED is always a detailed medical and sexological history of patients and partners when available (1,2). Often it is not possible to include the partner on the patient's first visit, but an effort should be made to include the partner at the second visit. The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 3) (3). Taking a comprehensive medical history may reveal one of the many common disorders associated with ED.

It is important to establish a relaxed atmosphere during history-taking. This will make it easier to ask questions about erectile function and other aspects of sexual history. A relaxed atmosphere will also make it easier to explain the diagnosis and therapeutic approach to the patient and his partner.

Table 3: Pathophysiology of ED

Vasculogenic	
-	Cardiovascular disease
-	Hypertension
-	Diabetes mellitus
-	Hyperlipidaemia
-	Smoking
-	Major surgery (RP) or radiotherapy (pelvis or retroperitoneum)
Neurogenic	
Central causes	
-	Degenerative disorders (multiple sclerosis, Parkinson's disease, multiple atrophy etc.)
-	Spinal cord trauma or diseases
-	Stroke
-	Central nervous system tumours
Peripheral causes	
-	Type 1 and 2 diabetes mellitus
-	Chronic renal failure
-	Polyneuropathy
-	Surgery (pelvis or retroperitoneum, radical prostatectomy, colorectal surgery, etc.)
Anatomical or structural	
-	Hypospadias, epispedias
-	Micropenis
-	Congenital curvature of the penis
-	La Peyronie's disease
Hormonal	
-	Hypogonadism
-	Hyperprolactinemia
-	Hyper- and hypothyroidism
-	Hyper- and hypocortisolism (Cushing's disease etc.)

Drug-induced	
-	Antihypertensives (diuretics are the most common medication causing ED)
-	Antidepressants (selective serotonin reuptake inhibitors, tricyclics)
-	Antipsychotics (incl. neuroleptics)
-	Antiandrogens; GnRH analogues and antagonists
-	Recreational drugs (alcohol, heroin, cocaine, marijuana, methadone)
Psychogenic	
-	Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
-	Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma	
-	Penile fracture

2.2.1.1 Sexual history

The sexual history must include (when available) information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. The sexual health status of the partner(s) (when available) can also be useful. A detailed description should be made of the rigidity and duration of both sexually stimulated and morning erections and of problems with arousal, ejaculation, and orgasm. Validated psychometric questionnaires, such as the International Index for Erectile Function (IIEF) (4), help to assess the different sexual function domains (i.e., sexual desire, erectile function, orgasmic function, ejaculation, intercourse, and overall satisfaction), as well as the impact of a specific treatment modality. Psychometric analysis also supports the use of erectile hardness score as a simple, reliable and valid tool for the assessment of penile rigidity in practice and in clinical trials research (5). In cases of clinical depression, the use of a 2-question scale for depression is recommended: “During the past month have you often been bothered by feeling down, depressed or hopeless? During the past month have you often been bothered by little interest or pleasure, doing things?” (6). Patients should be screened for symptoms of possible hypogonadism, including decreased energy, libido, fatigue, and cognitive impairment, as well as for symptomatic lower urinary tract symptoms. Where indicated, screening questionnaires, such as the International Prostate Symptom Score may be utilised.

2.2.1.2 Physical examination

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular, and neurological systems (1). A physical examination may reveal unsuspected diagnoses, such as La Peyronie’s disease, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggesting hypogonadism (small testes, alterations in secondary sexual characteristics etc.) (2). A rectal examination should be performed in every patient older than 40 years. Blood pressure and heart rate should be measured if they have not been assessed in the previous 3-6 months. Particular attention must be given to patients with cardiovascular disease (Section 2.2.2).

2.2.1.3 Laboratory testing

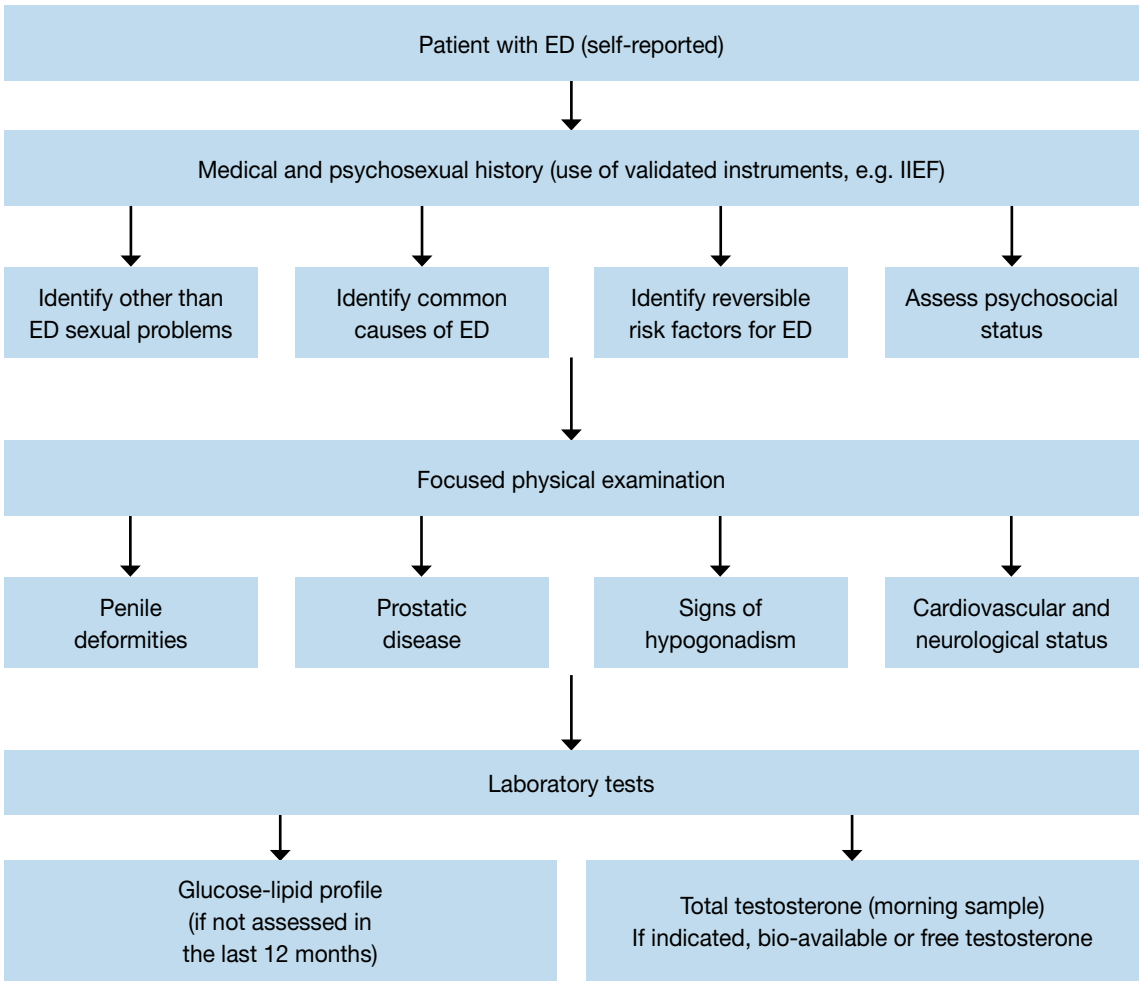
Laboratory testing must be tailored to the patient’s complaints and risk factors. Patients may need a fasting glucose or HbA1c and lipid profile if not recently assessed. Hormonal tests include a morning sample of total testosterone. If indicated bioavailable or calculated-free testosterone may be needed to corroborate total testosterone measurements. However, the threshold of testosterone to maintain ED is low and ED is usually a symptom of more severe cases of hypogonadism (7). For levels > 8 nmol/l the relationship between circulating testosterone and sexual function is very low (7,8).

Additional laboratory tests may be considered in selected patients, for example, prostate-specific antigen (PSA) for detection, or suspicion, of prostate cancer (9). Additional hormonal tests, for example, prolactin, and luteinizing hormone, are performed when low testosterone levels are detected. If any abnormality is observed, referral to an endocrinologist may be indicated (10,11).

Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, these opportunities to identify critical comorbid conditions should not be missed (12).

Figure 1 gives the minimal diagnostic evaluation (basic work-up) in patients with ED.

Figure 1: Minimal diagnostic evaluation (basic work-up) in patients with ED



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

*2.2.2 **Cardiovascular system and sexual activity: the patient at risk***

Patients who seek treatment for sexual dysfunction have a high prevalence of cardiovascular disease. The cardiac risks associated with sexual activity are well established. Epidemiological surveys have emphasised the association between cardiovascular and metabolic risk factors and sexual dysfunction in men and women (13). ED can improve the sensitivity of screening for asymptomatic cardiovascular disease in men with diabetes (14,15). ED significantly increases the risk of cardiovascular disease, coronary heart disease, stroke, and all-cause mortality, and the increase is probably independent of conventional cardiovascular risk factors (16).

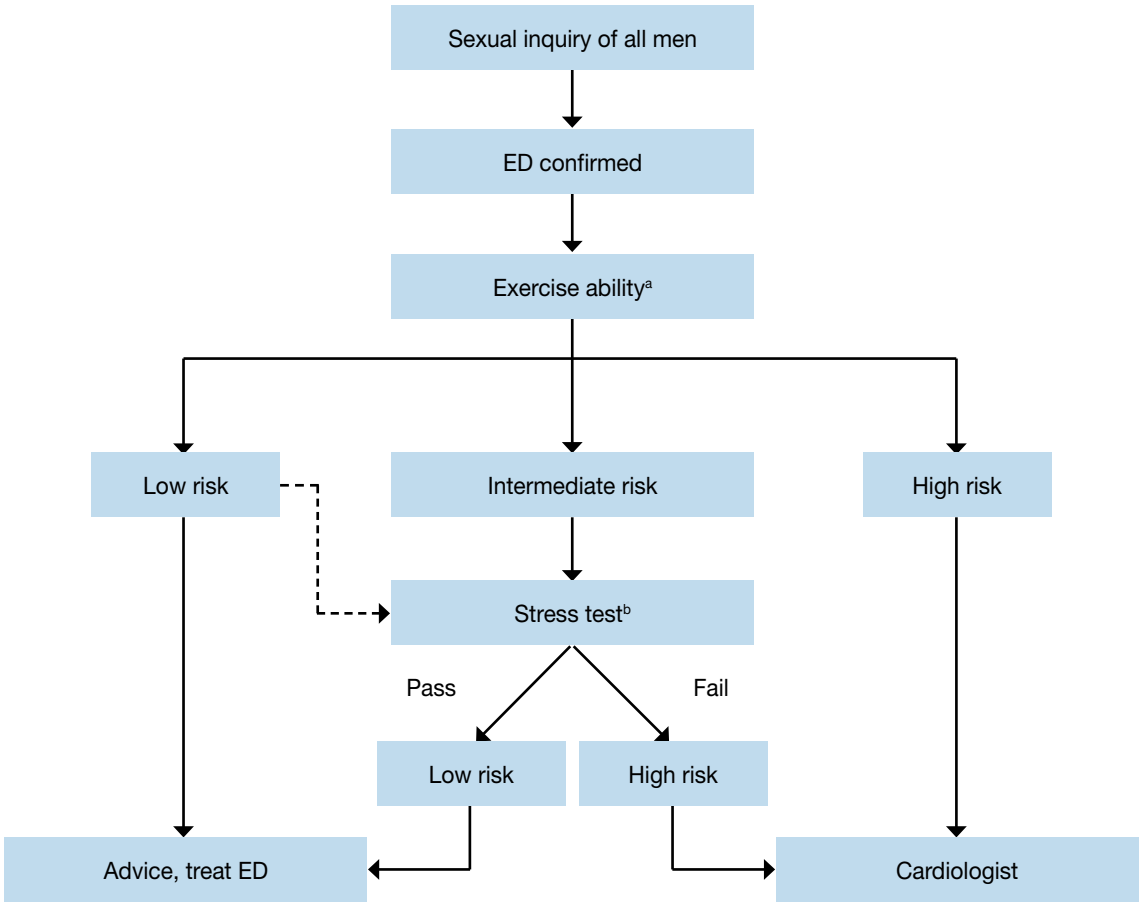
There has been an extensive investigation of the pharmacological properties of phosphodiesterase 5 inhibitors (PDE5Is), including their effects on cardiac smooth muscle activity and overall cardiovascular safety. The EAU Guidelines for treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk (17-19). The Princeton Consensus (Expert Panel) Conference is dedicated to optimizing sexual function and preserving cardiovascular health. A total of three consensus papers have been published (17-19). The Third Princeton Consensus had two primary objectives. The first focused on evaluation and management of cardiovascular risk in men with ED and no known cardiovascular disease, with particular emphasis on identification of men with ED who may require additional cardiological work-up. The second objective focused on re-evaluation and modification of previous recommendations for evaluation of cardiac risk associated with sexual activity in men with known cardiovascular disease. The recommendations built on those developed during the first and second Princeton Consensus Conferences; first, emphasising the use of exercise ability and stress testing to ensure that each man's cardiovascular health is consistent with the physical demands of sexual activity before prescribing treatment for ED; and second, highlighting the link between ED and cardiovascular disease, which may be asymptomatic and benefit from cardiovascular risk reduction (19). Patients with ED can be stratified into three cardiovascular risk categories (Table 4), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 2). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, which can be determined when taking the patient's history.

Table 4: Cardiac risk stratification (based on 2nd Princeton Consensus) (18)

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Figure 2: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) (19)



[a]Sexual activity is equivalent to walking 1 mile on the flat in 20 min or briskly climbing two flights of stairs in 10 s.
[b]Sexual activity is equivalent to 4 min of the Bruce treadmill protocol.

2.2.2.1 *Low-risk category*

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. Low risk is typically implied by the ability to perform exercise of modest intensity, which is defined as ≥ 6 "metabolic equivalents of energy expenditure in the resting state" (METs) without symptoms. According to current knowledge of the exercise demand or emotional stress associated with sexual activity, low-risk patients do not need cardiac testing or evaluation before the initiation or resumption of sexual activity or therapy for sexual dysfunction.

2.2.2.2 *Intermediate- or indeterminate-risk category*

The intermediate- or indeterminate-risk category consists of patients with an uncertain cardiac condition or patients whose risk profile requires testing or evaluation before the resumption of sexual activity. Based upon the results of testing, these patients may be moved to either the high- or low-risk group. A cardiology consultation may be needed in some patients to help the primary physician determine the safety of sexual activity.

2.2.2.3 *High-risk category*

High-risk patients have a cardiac condition that is sufficiently severe and/or unstable for sexual activity to carry a significant risk. Most high-risk patients have moderate-to-severe symptomatic heart disease. High-risk individuals should be referred for cardiac assessment and treatment. Sexual activity should be stopped until the patient's cardiac condition has been stabilised by treatment, or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

2.2.3 ***Specialised diagnostic tests***

Most patients with ED can be managed within the sexual care setting, conversely, some patients may need specific diagnostic tests (Tables 5 and 6).

2.2.3.1 *Nocturnal penile tumescence and rigidity test*

The nocturnal penile tumescence and rigidity (NPTR) assessment should be done on at least two nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for ≥ 10 min (20).

2.2.3.2 *Intracavernous injection test*

The intracavernous injection test gives limited information about vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 min after the intracavernous injection and lasts for 30 min (21). This response indicates a functional, but not necessarily normal, erection, and the erection may coexist with arterial insufficiency and/or veno-occlusive dysfunction (22). A positive test shows that a patient will respond to the intracavernous injection programme. The test is inconclusive as a diagnostic procedure and duplex Doppler study of the penis should be requested, if clinically warranted.

2.2.3.3 *Duplex ultrasound of the penis*

A peak systolic blood flow > 30 cm/s, an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 are generally considered normal (21). Further vascular investigation is unnecessary when a Duplex examination is normal.

2.2.3.4 *Arteriography and dynamic infusion cavernosometry or cavernosography*

Arteriography and dynamic infusion cavernosometry or cavernosography (DICC) should be performed only in patients who are being considered for vascular reconstructive surgery (23).

2.2.3.5 *Psychiatric assessment*

Patients with psychiatric disorders must be referred to a psychiatrist who is particularly interested in ED. In younger patients (< 40 years) with long-term primary ED, psychiatric assessment may be helpful before any organic assessment is carried out.

2.2.3.6 *Penile abnormalities*

Surgical correction may be needed for patients with ED due to penile abnormalities, e.g. hypospadias, congenital curvature, or Peyronie's disease with preserved rigidity.

2.2.4 ***Patient education - consultation and referrals***

Consultation with the patient should include a discussion of the expectations and needs of both the patient and his stable sexual partner, if available. It should also review both the patient's and partner's understanding

of ED, the results of diagnostic tests, and provide a rational selection of treatment options. Patient and partner education is an essential part of ED management (24,25).

Table 5: Indications for specific diagnostic tests

Primary ED (not caused by organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery.
Patients with penile deformities that might require surgical correction, e.g., Peyronie's disease, congenital curvature.
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or his partner.
Medicolegal reasons, e.g., implantation of penile prosthesis, sexual abuse.

Table 6: Specific diagnostic tests

NTPR using Rigiscan
Vascular studies
- Intracavernous vasoactive drug injection
- Duplex Doppler study of the penis
- Dynamic Infusion Cavernosometry and Cavernosography (DICC)
- Internal pudendal arteriography
Neurological studies, e.g., bulbocavernosus reflex latency, nerve conduction studies
Endocrinological studies
Specialised psychodiagnostic evaluation

*2.2.5 **Guidelines for the diagnostic evaluation of ED***

	LE	GR
Clinical use of validated questionnaire related to ED may help to assess all sexual function domains and the effect of a specific treatment modality.	3	B
Physical examination is needed in the initial assessment of men with ED to identify underlying medical conditions that may be associated with ED.	4	B
Routine laboratory tests, including glucose-lipid profile and total testosterone, are required to identify and treat any reversible risk factors and lifestyle factors that can be modified.	4	B
Specific diagnostic tests are indicated by only a few conditions.	4	B

*2.2.6 **References***

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3. TREATMENT OF ERECTILE DYSFUNCTION

3.1 Treatment options

The primary goal in the management strategy of a patient with ED is to determine its etiology and treat it when possible, and not to treat the symptom alone. ED may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors. These factors may be modified either before, or at the same time as, specific therapies are used.

As a rule, ED can be treated successfully with current treatment options, but cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g., hypogonadism and hyperprolactinaemia), which potentially can be cured with specific treatment.

Most men with ED will be treated with therapeutic options that are not cause specific. This results in a structured treatment strategy that depends on efficacy, safety, invasiveness and cost, as well as patient preference (1). To properly counsel patients with ED, physicians must be fully informed of all available treatment options. In this context, physician-patient (partner) dialogue is essential throughout the management of ED.

The assessment of treatment options must consider patient and partner satisfaction and other QoL factors as well as efficacy and safety. A treatment algorithm for ED is given in Figure 3.

3.2 Lifestyle management in ED with concomitant risk factors

The basic work-up of the patient must identify reversible risk factors for ED. Lifestyle changes and risk factor modification must precede or accompany any pharmacological treatment.

The potential benefits of lifestyle changes may be particularly important in individuals with ED and specific comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension (2-4). Besides improving erectile function, aggressive lifestyle changes may also benefit overall cardiovascular and metabolic health, with recent studies supporting the potential of lifestyle intervention to benefit both ED and overall health (5,6).

Although further studies are needed to clarify the role of lifestyle changes in management of ED and related cardiovascular disease, lifestyle changes can be recommended alone or combined with PDE5 therapy. Some studies have suggested that the therapeutic effects of PDE5Is may be enhanced when other comorbidities or risk factors are aggressively managed (7). A significant improvement can be expected as soon as 3 months after initiating lifestyle changes (8).

However, these results have yet to be confirmed in well-controlled, long-term studies. As a result of the success of pharmacological therapy for ED, clinicians need to provide specific evidence for the benefits of lifestyle change, and hopefully, future research will show this.

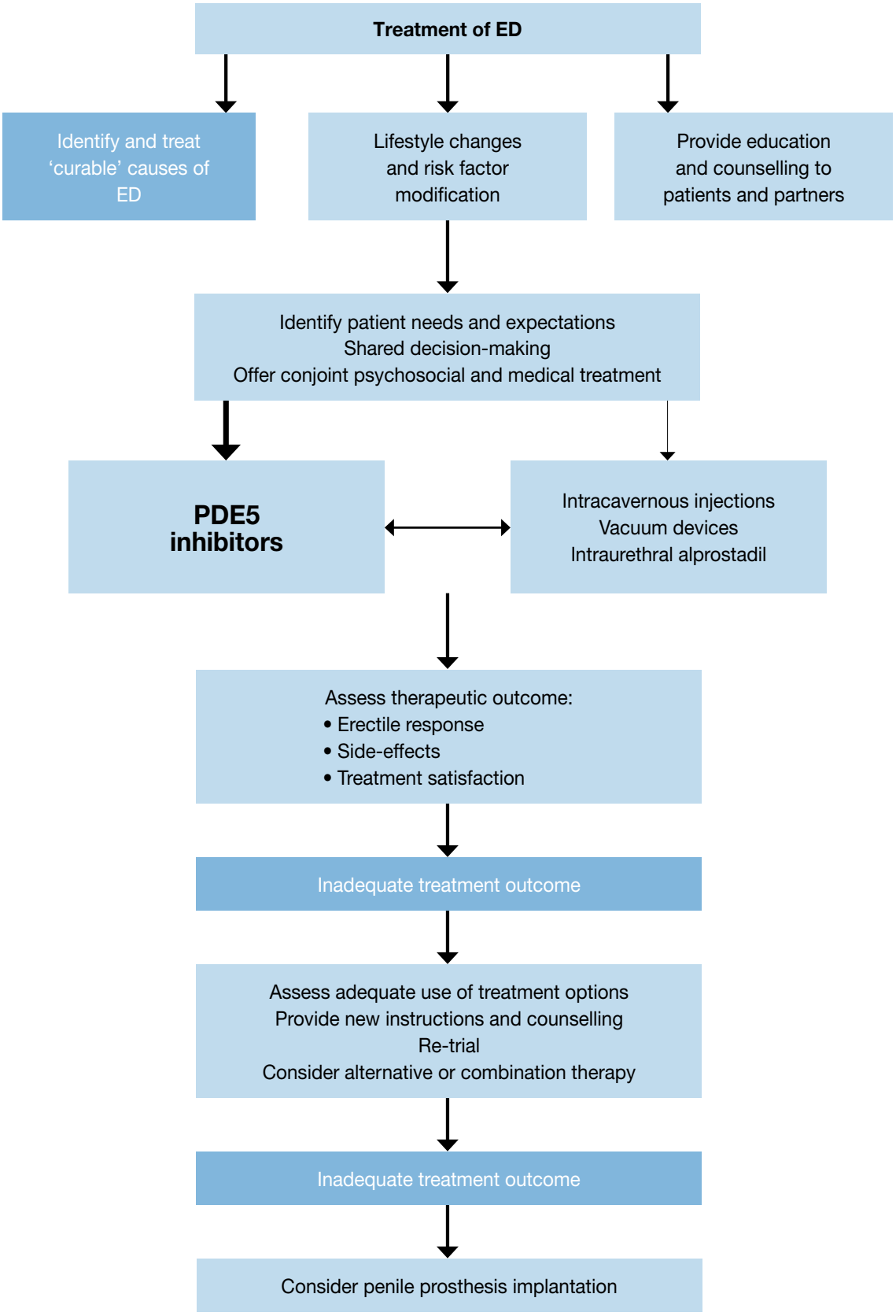
3.3 Erectile dysfunction after radical prostatectomy

Use of proerectile drugs following RP is important in achieving postoperative erectile function. Several trials have shown higher rates of erectile function recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED. Early compared with delayed erectile rehabilitation brings forward the natural healing time of potency (9).

Historically, the treatment options for postoperative ED have included intracavernous injections (10), urethral microsuppository (11), vacuum device therapy (12), and penile implants (13). Intracavernous injections and penile implants are still suggested as second- and third-line treatments, respectively, when oral compounds are not adequately effective or contraindicated for postoperative patients (Sections 3.6 and 3.7).

The management of post-RP ED has been revolutionised by the advent of PDE5Is, with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. Overall, it must be emphasized that post-RP ED patients are poor responders to PDE5Is. However, PDE5Is are the first-line choice of oral pharmacotherapy for post-RP ED in patients who have undergone nerve-sparing (NS) surgery. The choice of PDE5Is as first-line treatment is controversial because the experience (surgical volume) of the surgeon is a key factor in preserving postoperative erectile function, in addition to patient age and NS technique (14-16). In fact, PDE5Is are most effective in patients who have undergone a rigorous NS procedure,

Figure 3: Treatment algorithm for ED



which is more commonly performed by large-volume surgeons (14,15).

Early use of high-dose sildenafil after RP has been suggested to be associated with preservation of smooth muscle within the corpora cavernosa (17). Daily sildenafil also results in a greater return of spontaneous normal erectile function after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery (18,19). The response rate to sildenafil treatment for ED after RP in different trials has ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP (18-21).

Effectiveness of tadalafil and vardenafil as on-demand treatment has been evaluated in post-RP ED.

- A large multicentre trial in Europe and USA has studied tadalafil in patients with ED following bilateral NS surgery. Erectile function was improved in 71% of patients treated with 20 mg tadalafil versus 24% of those treated with placebo, while the rate of successful intercourse attempts was 52% with 20 mg tadalafil versus 26% with placebo (22).
- Similarly, vardenafil has been tested in patients with ED following either unilateral or bilateral NS surgery in a randomised, multicentre, prospective, placebo-controlled study in North America (23). Following bilateral NSRP, erectile function improved by 71% and 60% with 10 and 20 mg vardenafil, respectively. An extended analysis of the same patients undergoing NSRP has underlined the benefit of vardenafil compared to placebo regarding intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience (24).

A randomised, double-blind, double-dummy, multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on-demand and nightly dosing of vardenafil in men with ED following bilateral NSRP. In patients whose IIEF erectile function domain (IIEF-EF) score was $\geq$ 26 before surgery, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5Is in post-RP ED (25). A prospective, randomised, open label, multicentre American study in men with normal erection who underwent bilateral NSRP showed that oral and intraurethral treatment has the same benefit for penile recovery within the first year after surgery (26).

Patients who do not respond to oral PDE5Is after NSRP may be treated with prophylactic intracorporeal alprostadil (27,28). Penile prosthesis remains a satisfactory approach for patients who do not respond to either oral or intracavernous pharmacotherapy or to a vacuum device (29).

3.4 Causes of ED that can be potentially treated with a curative intent

*3.4.1 **Hormonal causes***

The advice of an endocrinologist may be beneficial for managing patients with hormonal abnormalities. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes, including a functional pituitary tumour resulting in hyperprolactinaemia.

Testosterone replacement therapy (intramuscular, oral, or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded (30). Testosterone replacement is controversial in men with a history of prostate carcinoma (LE: 4) (31). There is limited evidence suggesting that such treatment may not pose an undue risk of prostate cancer recurrence or progression (32). Before initiating testosterone replacement, digital rectal examination, serum PSA test, haematorcrit, liver function tests and lipid profile should be performed (33). Patients given androgen therapy should be monitored for clinical response, elevated haematorcrit and development of hepatic or prostatic disease. Testosterone therapy is contraindicated in patients with untreated prostate cancer or unstable cardiac disease.

*3.4.2 **Post-traumatic arteriogenic ED in young patients***

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate (34). The lesion must be demonstrated by duplex Doppler study of the penis and confirmed by penile pharmacoarteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by DICC. Vascular surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results (35).

*3.4.3 **Psychosexual counselling and therapy***

For patients with a significant psychological problem, psychosexual therapy may be given either alone or with another therapeutic approach. Psychosexual therapy requires ongoing follow-up and has had variable results (36).

3.5 First-line therapy

*3.5.1 **Oral pharmacotherapy***

PDE5 hydrolyses cGMP in the cavernosum tissue. Inhibition of PDE5 results in smooth muscle relaxation with increased arterial blood flow, leading to compression of the subtunical venous plexus and penile erection (37).

Three potent selective PDE5Is have been approved by the European Medicines Agency (EMA) for the treatment of ED. They are not initiators of erection and require sexual stimulation to facilitate an erection.

3.5.1.1 Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market. Efficacy is defined as an erection with rigidity sufficient for vaginal penetration. Sildenafil is effective from 30-60 min after administration. Its efficacy is reduced after a heavy, fatty meal due to prolonged absorption. It is administered in doses of 25, 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient's response and side effects. Efficacy may be maintained for up to 12 h (38). The pharmacokinetic data of sildenafil are presented in Table 7. Adverse events (Table 8) are generally mild in nature and self-limited by continuous use. The drop-out rate due to adverse events is similar to that with placebo (39).

After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% of a general ED population taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo (40). Sildenafil significantly improves patient scores in IIEF, sexual encounter profile (SEP)2, SEP3, and general assessment question (GAQ) and treatment satisfaction.

The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established. In patients with diabetes, 66.6% reported improved erections (GAQ) and 63% successful intercourse attempts compared to 28.6% and 33% of men taking placebo, respectively (41).

3.5.1.2 Tadalafil

Tadalafil was licenced for treatment of ED in February 2003 and is effective from 30 min after administration, with peak efficacy after about 2 h. Efficacy is maintained for up to 36 h (42) and is not affected by food. Ten and 20 mg doses have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side effects. Pharmacokinetic data of tadalafil are presented in Table 7. Adverse events (Table 8) are generally mild in nature and self-limited by continuous use. The drop-out rate due to adverse events is similar to that with placebo (43).

In premarketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 67% and 81% of a general ED population taking 10 and 20 mg tadalafil, respectively, compared to 35% of men in the control placebo group (43). Tadalafil significantly improves patient scores in IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. These results have been confirmed in postmarketing studies (44).

Tadalafil also improves erections in difficult-to-treat subgroups. In patients with diabetes, 64% reported improved erections (i.e., improved GAQ) versus 25% of patients in the control group, and the change in the final score for IIEF-EF was 7.3 compared to 0.1 for placebo (45). Nevertheless diabetic patients remain poor responders to tadalafil on demand, with a successful intercourse rates increasing from 21.8% with placebo to 45.4 and 49.9% with 10 and 20 mg of tadalafil on demand respectively (46).

3.5.1.3 Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 min after administration. Its effect is reduced by a heavy, fatty meal (> 57% fat). Five, 10 and 20 mg doses have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side effects. In vitro, it is 10-fold more potent than sildenafil, although this does not necessarily mean greater clinical efficacy (47). Pharmacokinetic data of vardenafil are presented in Table 7. Adverse events (Table 8) are generally mild in nature and self-limited by continuous use, with a drop-out rate similar to that with placebo (48).

After 12 weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of a general ED population taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo (49). Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in postmarketing studies (50).

Vardenafil improves erections in difficult-to-treat subgroups. In patients with diabetes, the final IIEF-EF score was 19 compared to 12.6 for placebo (51). Nevertheless, again, diabetic patients remain poor responders to vardenafil on-demand with a successful intercourse rates increasing from 23% with placebo to 49% and 54% with 10 and 20 mg of vardenafil on-demand, respectively (51).

Recently, a new formulation of vardenafil has been released, in the form of an orodispersable tablet (ODT). Orodispersable tablet formulations offer improved convenience over film-coated formulations and may be preferred by patients. Absorption is unrelated to food intake and they exhibit better bioavailability compared to film-coated tablets (52). The efficacy of vardenafil ODT has been demonstrated in several randomised controlled trials and did not seem to differ from the regular formulation (53-56).

3.5.1.4 Choice or preference between the different PDE5 inhibitors

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for sildenafil, tadalafil, and vardenafil. Choice of drug will depend on the frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, its possible disadvantages, and how to use it.

3.5.1.5 On-demand or chronic use of PDE5 inhibitors

Animal studies have shown that chronic use of PDE5Is improves or prevents significantly the intracavernous structure alterations due to age, diabetes, or surgical damage (57-62). No data exists for a human population.

In humans, a randomised study (n = 145) has shown that daily tadalafil led to a significantly higher IIEF-EF score and higher completion of successful intercourse attempts compared to on-demand tadalafil (63). Two major randomised double-blind studies, using 5 and 10 mg/day tadalafil for 12 weeks (n = 268) (64) and 2.5 and 5 mg/day tadalafil for 24 weeks (n = 286) (65), have shown that daily dosing was well tolerated and significantly improved erectile function. However, these studies lacked a comparative on-demand treatment arm. An open-label extension was carried out for both studies in 234 patients for 1 year and 238 patients for 2 years. Tadalafil, 5 mg once daily, was shown to be well tolerated and effective (66). Tadalafil, 5 mg once daily, therefore provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked. Nevertheless, in the 1-year open-label 5 mg tadalafil extension study followed by 4 weeks wash-out, erectile function was not maintained after discontinuation of therapy in most patients (about 75%).

In 2007, tadalafil 2.5 and 5 mg have been approved by the European Medicines Agency (EMA) for daily treatment of ED. According to EMA, patients who anticipate a frequent use of tadalafil (i.e., at least twice weekly) a once daily regimen with tadalafil 2.5 mg or 5 mg might be considered suitable, based on patient choice and the physician's judgement. In these patients, the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability. The appropriateness of the continuous use of a daily regimen should be reassessed periodically

A double-blind, placebo-controlled, multicentre, parallel-group study was conducted in 236 men with mild-to-moderate ED randomised to receive 10 mg vardenafil once daily plus on-demand placebo for 12 or 24 weeks, or once-daily placebo plus on-demand 10 mg vardenafil for 24 weeks, followed by 4 weeks wash-out (67). Despite preclinical evidence, the results suggested that once-daily dosing of 10 mg vardenafil does not offer any sustainable effect after cessation of treatment compared to on-demand administration in patients with mild-to-moderate ED.

Other studies (open-label, randomised, crossover studies with limited patient numbers) have shown that chronic, but not on-demand, tadalafil treatment improves endothelial function with a sustained effect after its discontinuation (68,69). This has been confirmed in another study of chronic sildenafil in men with type 2 diabetes (70).

Recently, in a double-blind, placebo-controlled study of 298 men with diabetes and ED, 2.5 and 5 mg tadalafil once daily for 12 weeks was efficacious and well tolerated. This regimen provides an alternative to on-demand treatment for some men with diabetes (71).

Table 7: Summary of the key pharmacokinetic data for the three PDE5 inhibitors used to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L
T_{max}	0.8-1 h	2 h	0.9 h
$T_{1/2}$	2.6-3.7 h	17.5 h	3.9 h
AUC	1685 µg.h/L	8066 µg.h/L	56.8 µg.h/L
Protein binding	96%	94%	94%
Bioavailability	41%	NA	15%

C_{max}: maximal concentration, T_{max}: time-to-maximum plasma concentration; $T_{1/2}$: plasma elimination halftime; AUC: area under curve or serum concentration time curve.

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics.*

Table 8: Common adverse events of the three PDE5 inhibitors used to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil
Headache	12.8%	14.5%	16%
Flushing	10.4%	4.1%	12%
Dyspepsia	4.6%	12.3%	4%
Nasal congestion	1.1%	4.3%	10%
Dizziness	1.2%	2.3%	2%
Abnormal vision	1.9%		< 2%
Back pain		6.5%	
Myalgia		5.7%	

** Adapted from EMA statements on product characteristics.*

Sildenafil: http://www.emea.europa.eu/humandocs/Humans/EPAR/viagra/viagra.htm
Tadalafil: http://www.emea.europa.eu/humandocs/Humans/EPAR/cialis/cialis.htm
Vardenafil: http://www.emea.europa.eu/humandocs/Humans/EPAR/levitra/levitra.htm

3.5.1.6 Safety issues for PDE5 inhibitors

3.5.1.6.1 Cardiovascular safety

Clinical trial results and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is, as part of either double-blind, placebo-controlled trials or open-label studies, or compared to expected rates in age-matched male populations.

None of the PDE5Is had an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina (72,73). In fact, they may even improve exercise tests. Sildenafil does not alter cardiac contractility, cardiac output or myocardial oxygen consumption according to available evidence. Chronic or on-demand use is well tolerated with a similar safety profile.

3.5.1.6.2 Nitrates are contraindicated with PDE5 inhibitors

Organic nitrates (e.g., nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) and other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate ("poppers" used for recreation), are absolute contraindications for the use of PDE5Is. They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used.

If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 h if sildenafil (and probably also vardenafil) is used (half-life, 4 h), and for at least 48 h if tadalafil is used (half-life, 17.5 h).

If a patient develops angina while taking a PDE5I, other agents may be given instead of nitroglycerine until the appropriate time has passed. If nitroglycerine must be reintroduced following administration of a PDEI, the patient should receive it only after an appropriate interval has elapsed, as described above, and under close medical observation.

3.5.1.6.3 Antihypertensive drugs

Co-administration of PDE5Is with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β-blockers, and diuretics) may result in small additive

decreases in blood pressure, which are usually minor. In general, the adverse event profile of a PDE5I is not made worse by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents.

3.5.1.6.4 α-Blocker interactions

All PDE5Is show some interaction with α-blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling currently advises that 50 or 100 mg sildenafil should be used with caution in patients taking an α-blocker (especially doxazosin). Hypotension is more likely to occur within 4 h following treatment with an α-blocker. A starting dose of 25 mg is recommended.
- Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his alpha-blocker therapy.
- Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension (74).
- Tadalafil is not recommended in patients taking doxazosin but this is not the case for tamsulosin, 0.4 mg (75).

These interactions are more pronounced when PDE5Is are given to healthy volunteers not previously taking α-blockers. Therefore, patients should be stable on α-blocker therapy prior to initiating combined treatment, and that the lowest dose should be started initially of PDE5Is. Further research is needed into the interaction between other PDE5Is and other α-blockers (e.g., alfuzosin, once-daily), or mixed α/β-blockers (e.g., carvedilol and labetalol).

3.5.1.6.5 Dosage adjustment

Drugs that inhibit the CYP34A pathway will inhibit the metabolic breakdown of PDE5Is. They include ketoconazole, itraconazole, erythromycin, clarithromycin, and HIV protease inhibitors (ritonavir and saquinavir). Such agents may increase blood levels of PDE5Is, so that lower doses of PDE5Is are necessary.

However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required.
Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

3.5.1.7 Management of non-responders to PDE5 inhibitors

The two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy of the drug. The management of non-responders depends upon identifying the underlying cause.

3.5.1.7.1 Check that the patient has been using a licensed medication

There is a large black market in PDE5Is. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication.

3.6.1.7.2 Check that the medication has been properly prescribed and correctly used

The main reason why patients fail to use their medication correctly is inadequate counselling from their physician. The main ways in which a drug may be incorrectly used are:

- failure to use adequate sexual stimulation;
- failure to use an adequate dose;
- failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

Lack of adequate sexual stimulation: PDE5I action is dependent on the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the drugs cannot work.

Oral PDE5Is take different times to reach maximal plasma concentrations (76,77). Although pharmacological activity is achieved at plasma levels well below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all three drugs have an onset of action in some patients within 30 min of oral ingestion, most patients require a longer delay between taking the medication, with at least 60 min being required for men using sildenafil and vardenafil, and up to 2 h being required for men using tadalafil (78-80).

Absorption of sildenafil can be delayed by a meal, and absorption of vardenafil can be delayed by a fatty meal (81). Absorption of tadalafil is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse (77).

It is possible to wait too long after taking medication before attempting sexual intercourse. The half-life

of sildenafil and vardenafil is about 4 h, suggesting that the normal window of efficacy is 6-8 h following drug ingestion, although responses following this time period are well recognised. Tadalafil has a longer half-life of ~17.5 h, so the window of efficacy is much longer at ~36 h.

For financial reasons, some physicians may prescribe only lower doses of a drug. It is important to check that the patient has had an adequate trial of the maximal dose of the drug. Data suggest an adequate trial involves at least six attempts with a particular drug (82).

Data from uncontrolled studies suggests patient education can help salvage an apparent non-responder to a PDE5I. After emphasising the importance of dose, timing, and sexual stimulation to the patient, erectile function can be effectively restored following re-administration of the relevant PDE5I (83-85).

One study (84) went further, and in those patients who still did not respond to the PDE5I, a second-line adjustment was instituted. Patients taking tadalafil were advised to wait at least 2 h between oral ingestion and attempting intercourse. Patients taking vardenafil were advised to use the drug only after a fast. In both patient groups, further apparent non-responders were salvaged. No patients using sildenafil were included in this study.

3.5.1.7.3 Possible manoeuvres in patients correctly using a PDE5 inhibitor

When the patient is using an adequate dose of the drug properly and the response is still inadequate, there are several changes that may improve drug efficacy, although the evidence supporting these interventions is limited.

Erectile dysfunction is typically a symptom of an underlying condition, such as diabetes, hypertension, or dyslipidaemia. There is evidence suggesting that, in patients with hypogonadism, normalisation of serum testosterone might improve response to a PDE5I (86). Modification of other risk factors may be also be beneficial as discussed in section 3.2.

A randomised trial has suggested that vardenafil benefits non-responders to sildenafil (87), but because of poor study design, the results are considered to overstate the benefits of switching PDE5Is. However, a randomised, open-label, crossover trial comparing sildenafil and tadalafil has indicated that some patients might respond better to one PDE5I than to another (88). According to the IIEF-EF score, 17% of patients had a better response (≥ 5 points) to tadalafil than to sildenafil, while 14% had a better response to sildenafil than tadalafil.

Although these differences might be explained by variation in drug pharmacokinetics, they do raise the possibility that, despite an identical mode of action, switching to a different PDE5I might be helpful.

Two non-randomized trials have suggested that daily dosing with a PDE5I might salvage some non-responders to intermittent dosing. In one trial (89), some men benefited from regular dosing with either vardenafil or tadalafil, while in the other trial (84) daily dosing with tadalafil salvaged some men who had failed to respond to intermittent dosing with a PDE5I.

Currently, there are no randomised trials to support this intervention. Although tadalafil is licensed for daily dosing at 2.5 and 5 mg, neither sildenafil nor vardenafil are licensed for use in this way.

If drug treatment fails, then patients should be offered an alternative therapy such as intracavernosal injection therapy or use of a vacuum erection device.

*3.5.2 **Vacuum erection devices***

Vacuum erection devices (VEDs) provide passive engorgement of the corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the corpora. Thus, erections with these devices are not normal because they do not use physiological erection pathways. Efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% (90). Men with a motivated, interested, and understanding partner report the highest satisfaction rates. Long-term use of VEDs decreases to 50-64% after 2 years (91). Most men who discontinue use of VEDs do so within 3 months.

The commonest adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in < 30% of patients (92). Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 min. VEDs are contraindicated in patients with bleeding disorders or on anticoagulant therapy.

VEDs may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED (90).

*3.5.3 **Shockwave therapy***

Recently, the use of low-intensity extracorporeal shock wave therapy was proposed as a novel treatment for ED (93). In the first randomised, double-blind, sham-controlled study, it was demonstrated that low-intensity extracorporeal shock wave therapy had a positive short-term clinical and physiological effect on the erectile function of men who respond to oral PDE5Is (94). Moreover, there are preliminary data showing improvement

in penile haemodynamics and endothelial function, as well as IIEF-EF domain score in severe ED patients who are poor responders to PDE5Is (95).The feasibility and tolerability of this treatment, coupled with its potential rehabilitative characteristics, make it an attractive new therapeutic option for men with ED. However, current data are limited and clear recommendations cannot be given. Data regarding the mechanism of action of this procedure are still lacking. In a diabetic rat model, low-intensity extracorporeal shock wave therapy ameliorated diabetes mellitus associated ED by promoting regeneration of nNOS-positive nerves, endothelium, and smooth muscle in the penis. These beneficial effects appear to be mediated by recruitment of endogenous mesechymal stem cells (MSCs) (96).

3.6 Second-line therapy

Patients not responding to oral drugs may be offered intracavernous injections. Success rate is high (85%) (97,98). Intracavernous administration of vasoactive drugs was the first medical treatment for ED more than 20 years ago (99).

*3.6.1 **Intracavernous injections***

3.6.1.1 Alprostadil

Alprostadil (CaverjectTM, Edex/ViridalTM) was the first and only drug approved for intracavernous treatment of ED (99). Intracavernous alprostadil is most efficacious as monotherapy at a dose of 5-40 µg; although the 40 µg dose is not registered in every European country. The erection appears after 5-15 min and lasts according to the dose injected. An office-training programme (one or two visits) is required for the patient to learn the correct injection process. In cases of limited manual dexterity, the technique may be taught to their partners. The use of an automatic special pen that avoids a view of the needle can resolve fear of penile puncture and simplifies the technique.

Efficacy rates for intracavernous alprostadil of > 70% have been found in general ED populations, as well as in patient subgroups (e.g., diabetes or cardiovascular disease), with reported sexual activity after 94% of the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners (100-102).

Complications of intracavernous alprostadil include penile pain (50% of patients reported pain but pain reported only after 11% of total injections), prolonged erections (5%), priapism (1%), and fibrosis (2%) (103). Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia (104,105). Cavernosal fibrosis (from a small hematoma) usually clears within a few months after temporary discontinuation of the injection program. However, tunical fibrosis suggests early onset of La Peyronie's disease and may indicate stopping intracavernosal injections indefinitely. Systemic side effects are uncommon. The most common is mild hypotension, especially when using higher doses.

Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders.

Despite these favourable data, intracavernous pharmacotherapy is associated with high drop-out rates and limited compliance. Drop-out rates of 41-68% have been described (106-108), with most drop-outs occurring within the first 2-3 months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy of 10% per year. Reasons for discontinuation included desire for a permanent modality of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop-out patients), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%). Careful counselling of patients during the office-training phase as well as close follow-up is important in addressing patient withdrawal from an intracavernous injection programme (109).

Today, intracavernous pharmacotherapy is considered a second-line treatment. Patients not responding to oral drugs may be offered intracavernous injections with a high success rate of 85%. Most long-term injection users can switch to sildenafil despite underlying pathophysiology (110-112). However, almost one-third of long-term intracavernous injection users who subsequently also responded to sildenafil preferred to continue with an intracavernous injection programme (112,113).

3.6.1.2 Combination therapy

Combination therapy enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating side effects by using lower doses of each drug.

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is most commonly used in combination therapy today due to its high incidence of side effects as monotherapy.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxisylyte or calcitonin gene-related peptide (CGRP), usually combined with the main drugs (114,115). Most combinations are not

standardised and some drugs have limited availability worldwide.

- Papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 µg), have been widely used with improved efficacy rates, although they have never been licensed for ED (116-118). The triple combination regimen of papaverine, phentolamine and alprostadil has the highest efficacy rates, reaching 92%; this combination has similar side effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on total dose). In addition, mild hepatotoxicity has been reported with papaverine (119).

Despite high efficacy rates, 5-10% of patients do not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone (120). However, combination therapy is associated with an incidence of adverse effects in 33% of patients, including dizziness in 20% of patients. This strategy can be considered in carefully selected patients before proceeding to a penile implant.

3.6.1.3 Intraurethral alprostadil

A specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) has been approved for use in ED (121). A vascular interaction between the urethra and the corpora cavernosa enables drug transfer between these structures (121). Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, only the higher doses (500 and 1000 µg) have been used with low consistency response rates (121-123). The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy (123,124).

The most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are very rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration.

Efficacy rates are significantly lower than intracavernous pharmacotherapy (125). Intraurethral pharmacotherapy is a second-line therapy and provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

3.7 Third-line therapy (penile prostheses)

The surgical implantation of a penile prosthesis may be considered in patients who do not respond to pharmacotherapy or who prefer a permanent solution to their problem. The two currently available classes of penile implants include inflatable (2- and 3-piece) and malleable devices (126-129).

Most patients prefer the three-piece inflatable devices due to the more “natural” erections obtained. The three-piece inflatable penile include a separate reservoir placed in the abdominal cavity. Three-piece devices provide the best rigidity and the best flaccidity because they will fill every part of the corporal bodies. However, the two-piece inflatable prosthesis can be a viable option among patients who are deemed high risk of complications with reservoir placements. Malleable prostheses result in a firm penis, which may be manually placed in an erect or flaccid state (126-129).

There are two main surgical approaches for penile prosthesis implantation: peno-scrotal and infrapubic (126-129). The penoscrotal approach provides an excellent exposure, it affords proximal crural exposure if necessary, avoids dorsal nerve injury and permits direct visualisation of pump placement. However, with this approach the reservoir is blindly placed into the retropubic space, which can be a problem in patients with a history of major pelvic surgery (mainly radical cystectomy). The infrapubic approach has the advantage of reservoir placement under direct vision but the implantation of the pump may be more challenging, and patients are at a slightly increased risk of dorsal nerve injury. Revision surgery is associated with decreased outcomes and may be more challenging.

*3.7.1 **Efficacy and satisfaction rates***

Prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED based on appropriate consultation (130-137). Mulhall and colleagues have used the IIEF and the Erectile Dysfunction Index for Treatment Satisfaction (EDITS) at 3-month intervals following implantation of inflatable penile prostheses. There was a continued improvement in scores for the IIEF and EDITS stabilised 9-12 months following surgery. All variables, including erection, ejaculation, orgasm, and overall sexual satisfaction, improved above baseline values at 1 year after surgery. However, at 3 months following surgery, the results were less satisfactory, suggesting that postoperative counselling and encouragement of patients is important to obtain ultimate satisfaction and positive outcomes at 9-12 months (134).

In a long-term multicentre study of the AMS 700CX three-piece inflatable prosthesis, with a median follow-up of 48 months, 79% of patients were using their device at least twice monthly and 88% would recommend the prosthesis to a friend or relative (135). In another multicentre study with 59 months follow-up,

at almost 5 years after surgery, 92.5% of patients were using their prosthesis an average of 1.7 times weekly and excellent or satisfactory results were reported by patients and their partners (132).

Increasingly, in patients with favourable prognosis after RP for prostate cancer, the presence of urinary incontinence and sexual dysfunction (primarily ED and orgasmic dysfunction) is leading doctors to the need for global management of both conditions. Based on appropriate clinical and diagnostic assessments of severity of adverse outcomes depending on patient preference, combination surgery for treatment of ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established, definitive role to address this problem (138).

*3.7.2 **Complications***

The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used three-piece prosthesis (AMS 700CX/CXR™ and Coloplast Alpha I™) resulted in mechanical failure rates of < 5% after 5 years follow-up (135,139). Careful surgical technique with proper antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduces infection rates to 2-3% with primary implantation in low-risk patients. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast itan™) (140-143).

Higher risk populations include patients undergoing revision surgery, those with impaired host defenses (immunosuppression, diabetes mellitus, spinal cord injury) or those with penile corporal fibrosis (126-129). Although diabetes is considered to be one of the main risk factors for infection, this is not supported by current data (126-129). Infections, as well as erosions, are significantly higher (9%) in patients with spinal cord injuries (9%) (126-129). Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate replacement with a new prosthesis has been described using a washout protocol with successful salvages achieved in > 80% of cases (144,145). The majority of revisions are secondary to mechanical failure and combined erosion or infection. Overall, 93% of cases are successfully revised, providing functioning penile prosthesis.

*3.7.3 **Conclusions***

Penile implants are an attractive solution for patients who do not respond to more conservative therapies. There is enough evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rates.

3.8 Guidelines for the treatment of ED

	LE	GR
Lifestyle changes and risk factor modification must precede or accompany ED treatment.	1a	A
Pro-erectile treatments have to be given at the earliest opportunity after RP.	1b	A
When a curable cause of ED is found, it must be treated first.	1b	B
PDE5Is are first-line therapy.	1a	A
Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5Is.	3	B
A VED can be used in patients with a stable relationship.	4	C
Intracavernous injection is second-line therapy.	1b	B
Penile implant is third-line therapy.	4	C

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4. PREMATURE EJACULATION (PE)

4.1 Introduction

Although PE is a very common male sexual dysfunction, it is poorly understood. Patients are often unwilling to discuss their symptoms and many physicians do not know about effective treatments. As a result, patients may be misdiagnosed or mistreated (1).

These guidelines provide an evidence-based analysis (2) of published data on definition, clinical evaluation and treatment. It provides recommendations to help clinicians with the diagnosis and treatment of PE.

4.2 Definition of PE

4.2.1 ***Overview***

There have previously been two official definitions of PE, neither of which have been universally accepted:

- In the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR), PE is defined as a '*persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity*' (3).
- In the World Health Organization's International Classification of Diseases-10 (ICD-10), PE is defined as '*the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity*' (4).

More recently, two more definitions have been proposed:

- The Second International Consultation on Sexual and Erectile Dysfunction defined PE as '*ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress, and over which the sufferer has little or no voluntary control*' (5).
- The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of PE which is the first evidence-based definition, '*Premature ejaculation is a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy*'. It must be noted that this definition is limited to men with lifelong PE who engage in vaginal intercourse since there are insufficient objective data to propose an evidence-based definition for acquired PE (6).

All four definitions have taken into account the time to ejaculation, the inability to control or delay ejaculation, and negative consequences (bother/distress) from PE. However, the major point of debate is quantifying the time to ejaculation, which is usually described by intravaginal ejaculatory latency time (IELT). Several proposals for updating the definition of PE in the forthcoming DSM-V and ICD-11 have been presented (7-11).

4.2.2 ***Classifications***

Premature ejaculation is classified as 'lifelong' (primary) or 'acquired' (secondary) (12).

- Lifelong PE is characterized by onset from the first sexual experience, remains so during life and ejaculation occurs too fast (before vaginal penetration or < 1-2 min after).

- Acquired PE is characterized by a gradual or sudden onset following normal ejaculation experiences before onset and time to ejaculation is short (usually not as short as in lifelong PE).

Recently, two more PE syndromes have been proposed (11):

- 'Natural variable PE' is characterized by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- 'Premature-like ejaculatory dysfunction' is characterized by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology.

The addition of these new types may aid patient stratification, diagnosis and treatment, but their exact role remains to be defined (13).

4.3 Epidemiology of PE

*4.3.1 **Prevalence***

The major problem in assessing the prevalence of PE is the lack of an accurate (validated) definition at the time the surveys were conducted (14). However, epidemiological research has consistently shown that PE, at least according to the DSM-IV definition, is the most common male sexual dysfunction, with prevalence rates of 20-30% (15-17).

The highest prevalence rate of 31% (men aged 18-59 years) was found by the National Health and Social Life Survey (NHSLS) study in USA (16). Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). These high prevalence rates may be a result of the dichotomous scale (yes/ no) in a single question asking if ejaculation occurred too early, as the prevalence rates in European studies have been significantly lower. A British self-completed mailed questionnaire survey estimated that the prevalence rate of PE was between 14% (3 months) and 31% (life-time) (18). A French telephone survey of men aged 40 to 80 years estimated the prevalence of premature ejaculation at 16% (19). A Swedish interview reported an overall prevalence rate of 9% in men aged 18 to 74 years (20), with prevalence by age being 4% (18-24 years), 7% (25-34 years), 8% (35-49 years), 8% (50-65 years) and 14% (66-74 years). A Danish study about sexual problems using a questionnaire (12 questions) and an interview (23 questions) reported the prevalence rate for PE to be 14% in men aged 51 years (21) while in another Danish random population survey using a structured personal interview the prevalence rates of PE were 7% in men aged 16-95 years (22). An Italian questionnaire-based survey in andrological centres recorded a prevalence rate of 21% (23). In a self-administered questionnaire-based survey in the Netherlands, the prevalence rate was 13% in men aged 50-78 years (24).

The prevalence of PE in the Premature Ejaculation Prevalence and Attitudes (PEPA) survey (a multinational, internet-based survey) was 22.7% (24.0% in the USA, 20.3% in Germany, and 20.0% in Italy) (17). The Global Study of Sexual Attitudes and Behaviors (GSSAB) survey was conducted in men between 40 and 80 years old in 29 different countries using personal and telephone interviews and self-completed mailed questionnaires; it confirmed that the worldwide prevalence of PE was almost 30%. Except for a low reported rate of PE in Middle Eastern countries (10-15%), prevalence was relatively similar throughout the rest of the world (15). The prevalence rate of PE was 18% in a five-country European Observational study using the IELT and the Premature Ejaculation Profile (PEP) (25), comparable to those obtained in a similarly designed US observational study (26).

Two studies reported on PE prevalence rates based on the Premature Ejaculation Diagnostic Tool (PEDT) (27,28). A computer-assisted interviewing, online, or in-person survey in nine countries in the Asia-Pacific region reported prevalence rates of 16% (premature ejaculation), 15% (probable PE) and 13% (self-reported PE) (27). Another study at a primary care clinic in Malaysia reported prevalence rates of 20.3% for PE and 20.3% for probable PE (28).

Finally, the only study reporting prevalence of all four proposed classifications of PE was a non-interventional, observational, cross-sectional field survey conducted in Turkey (29). Overall, the prevalence rate of PE was 20%. The prevalence rates were 2.3% (lifelong), 3.9% (acquired PE), 8.5% (natural variable PE) and 5.1% (premature-like ejaculatory dysfunction).

Further research is needed on the prevalence of lifelong and acquired PE. Limited data suggests that the prevalence of lifelong PE, defined as IELT < 1-2 min, is about 2-5% (20,26). These results are supported by the moderate genetic influence on PE (30) and low prevalence rates of IELT < 1 minute (31).

*4.3.2 **Pathophysiology and risk factors***

The aetiology of PE is unknown, with little data to support suggested biological and psychological hypotheses, including anxiety, penile hypersensitivity, and 5-HT receptor dysfunction (5). In addition, the pathophysiology of PE is largely unknown. In contrast to ED, there is no impairment of the physiological events leading up to the

forceful expulsion of sperm at the urethral meatus.

A significant proportion of men with ED also experience PE (15). High levels of performance anxiety related to ED may worsen PE, with a risk of misdiagnosing PE instead of the underlying ED.

According to the NHLS, the prevalence of PE is not affected by age (16,17), unlike ED, which increases with age. Premature ejaculation is not affected by marital or income status (16). However, PE is more common in blacks, Hispanic men and men from Islamic backgrounds (32,33) and may be higher in men with a lower educational level (15,16). Other risk factors may include a genetic predisposition (34), poor overall health status and obesity (16), prostate inflammation (35,36), thyroid hormone disorders (37), emotional problems and stress (16,38), and traumatic sexual experiences (15,16).

In the only published study on risk modification/prevention strategies (39), successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in IELT and ejaculatory control compared to untreated patients.

4.4 Impact of PE on QoL

Men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less frequent intercourse (40,41). However, the negative impact of PE extends beyond sexual dysfunction. PE can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression (40,42). Sex drive and overall interest in sex does not appear to be affected by PE (43). However, the partner's satisfaction with the sexual relationship decreased with increasing severity of the man's condition (44).

Despite the possible serious psychological and QoL consequences of PE, few men seek treatment. In the GSSAB survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems (15), with men more likely to seek treatment for ED than for PE (15). In the PEPA survey, only 9% of men with self-reported PE consulted a doctor (17).

The main reasons for not discussing PE with their physician are patient embarrassment and a belief that there is no treatment. Physicians are often uncomfortable discussing sexuality with their patients usually because of embarrassment and a lack of training or expertise in treating PE (45,46). Physicians need to encourage their patients to talk about PE.

4.5 Diagnosis of PE

Diagnosis of PE is based on the patient's medical and sexual history (47,48). History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the duration time of ejaculation, degree of sexual stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED.

Many patients with ED develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection (49). Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE (50).

There are several overlapping definitions of PE (see 4.2.1), with four shared factors (Table 7), resulting in a multidimensional diagnosis (51).

Table 7: Common factors in different definitions of ED

• Time to ejaculation assessed by IELT
• Perceived control
• Distress
• Interpersonal difficulty related to the ejaculatory dysfunction

4.5.1 Intravaginal ejaculatory latency time (IELT)

The use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE (25, 26). Moreover, IELT has a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse (52). In addition, perceived control over ejaculation has a significant direct effect on both ejaculation-related personal distress and satisfaction with sexual intercourse (each showing direct effects on interpersonal difficulty related to ejaculation).

In everyday clinical practice, self-estimated IELT is sufficient (53). Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity (54). Specificity can be improved further to 96% by combining IELT with a single-item patient-reported outcome (PRO) on control over ejaculation and satisfaction with sexual intercourse (scale ranging from 0 = very poor to

4 = very good) and on personal distress and interpersonal difficulty (0 = not at all to 4 = extremely). However, stopwatch-measured IELT is necessary in clinical trials. While IELT is an objective tool for PE assessment, a recent study reported that sexual satisfaction and distress correlated more strongly with the feeling of control than with the self-reported latency time (55).

*4.5.2 **PE assessment questionnaires***

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs (51). Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT): five-item questionnaire based on focus groups and interviews from the USA, Germany and Spain. Assesses control, frequency, minimal stimulation, distress and interpersonal difficulty (56,57). A total score ≥ 11 suggests a diagnosis of PE, a score of 9 or 10 suggests a probable diagnosis of PE while a score of ≤ 8 indicates a low likelihood of PE.
- Arabic Index of Premature Ejaculation (AIPE): seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction for the patient and partner, anxiety or depression (58). A cutoff score of 30 (range of scores 7-35) discriminated best PE diagnosis. Severity of PE was classified as severe (score: 7-13), moderate (score: 14-19), mild to moderate (score: 20-25) and mild (score: 26-30).

The most widely used tool is the PEDT. However, there is a low correlation between a diagnosis provided by PEDT and a self-reported diagnosis. A recent study reported that only 40% of men with PEDT-diagnosed PE and 19% of men with probable PE self-reported the condition (27). A sexual health survey conducted by the Turkish Society of Andrology reported that, although the sensitivity values of PEDT and AIPE were 89.3% and 89.5%, respectively, the specificity values were only 50.5% and 39.1%, respectively (59). Moreover, there were statistically significant differences in detection rates of PEDT and AIPE among the four PE syndromes, being higher in acquired and lifelong PE and lower in natural variable PE and premature-like ejaculatory dysfunction.

These tools are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed (60).

Other questionnaires used to characterize PE and determine treatment effects include the PEP (26), Index of Premature Ejaculation (IPE) (61) and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) (62). Currently, their role is optional in everyday clinical practice.

*4.5.3 **Physical examination and investigations***

Physical examination may be part of the initial assessment of men with PE. It may include a brief examination of the endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as endocrinopathy, Peyronie's disease, urethritis or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended (48).

4.6 Recommendations

Recommendations	LE	GR
Diagnosis and classification of PE is based on medical and sexual history. It should be multidimensional and assess IELT, perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	1a	A
Clinical use of self-estimated IELT is adequate. Stopwatch-measured IELT is necessary in clinical trials.	2a	B
Patient-reported outcomes (PROs) have the potential to identify men with PE. Further research is needed before PROs can be recommended for clinical use.	3	C
Physical examination may be necessary in initial assessment of PE to identify underlying medical conditions that may be associated with PE or other sexual dysfunctions, particularly ED.	3	C
Routine laboratory or neurophysiological tests are not recommended. They should only be directed by specific findings from history or physical examination.	3	C

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4.8 Treatment

In men for whom PE causes few, if any problems, treatment is limited to psychosexual counselling and education. Before beginning treatment, it is essential to discuss patient expectations thoroughly. Furthermore, it is important to treat first, if present, erectile dysfunction especially and prostatitis.

Various behavioural techniques have been beneficial in treating PE and are indicated for patients uncomfortable with pharmacological therapy. In lifelong PE, behavioural techniques are not recommended for first-line treatment. They are time-intensive, require the support of a partner and can be difficult to perform. In addition, long-term outcomes of behavioural techniques for PE are unknown.

Pharmacotherapy is the basis of treatment in lifelong PE. Dapoxetine is the only on-demand pharmacological treatment approved for PE in European countries; all other medications used in PE are off-label indications. Chronic antidepressants including selective serotonin reuptake inhibitors (SSRIs) and clomipramine, a tricyclic antidepressant and on-demand topical anaesthetic agents have consistently shown efficacy in PE. Long-term outcomes for pharmacological treatments are unknown.

An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grade of recommendation are provided and a treatment algorithm is presented (Figure 4).

*4.8.1 **Psychological/behavioural strategies***

Behavioural strategies mainly include the ‘stop-start’ programme developed by Semans (1) and its modification, the ‘squeeze’ technique, proposed by Masters and Johnson:

- In the ‘stop-start’ programme, the partner stimulates the penis until the patient feels the urge to ejaculate. At this point, he instructs his partner to stop, waits for the sensation to pass and then stimulation is resumed.
- The ‘squeeze’ technique is similar but the partner applies manual pressure to the glans just before ejaculation until the patient loses his urge.

Both these procedures are typically applied in a cycle of three pauses before proceeding to orgasm. Behavioural strategies are based on the hypothesis that PE occurs because the man fails to appreciate the sensations of heightened arousal and to recognise the feelings of ejaculatory inevitability. Re-training may attenuate stimulus-response connections by gradually exposing the patient to progressively more intense and more prolonged stimulation, while maintaining the intensity and duration of the stimulus just below the threshold for triggering the response. There are several modifications of these techniques making comparison difficult.

Masturbation before anticipation of sexual intercourse is a technique used by younger men. Following masturbation, the penis is desensitized resulting in greater ejaculatory delay after the refractory period is over. In a different approach, the man learns to recognise the signs of increased sexual arousal and how to keep his level of sexual excitement below the intensity that elicits the ejaculatory reflex. Efficacy is similar to the ‘start-stop’ programme (2).

Psychological factors may be associated with PE and should be addressed in treatment. These factors, if any, mainly relate to anxiety, but could also include relationship factors. The limited studies available suggest that behavioural therapy, as well as functional sexological treatment lead to improvements in the duration of intercourse and sexual satisfaction.

Overall, short-term success rates of 50-60% have been reported (3,4). However, there is no controlled research to support the efficacy of behavioural techniques, while a double-blind, randomized, crossover study showed that pharmacological treatment (chlomipramine, sertraline, paroxetine and sildenafil) resulted in greater IELT prolongation than behavioural therapy (5). Furthermore, clinical experience suggests that improvements achieved with these techniques are generally not maintained long term (6,7). Behavioural therapy may be most effective when used to 'add value' to medical interventions, although this suggestion requires proof from further randomized clinical trials. Validated assessment instruments need to be used as end-points. Longer follow-up periods are necessary to confirm these findings.

4.8.1.1 Guideline recommendation

Treatment of PE	LE	GR
Psychological/behavioural therapies	3	C

*4.8.2 **Dapoxetine***

Dapoxetine hydrochloride is a short-acting SSRI, with a pharmacokinetic profile suitable for on-demand treatment for PE. It has a rapid Tmax (1.3 hours) and a short half-life (95% clearance rate after 24 hours) (8). Dapoxetine has been investigated in 6081 subjects to date (9). It is approved for on-demand treatment of PE in European countries and elsewhere, but not in the USA.

Both available doses of dapoxetine (30 mg and 60 mg) have shown 2.5- and 3.0-fold increases, respectively, in IELT overall, rising to 3.4- and 4.3-fold in patients with baseline average IELT < 0.5 minutes (10,11). In RCTs, dapoxetine, 30 mg or 60 mg 1-2 hours before intercourse, was effective from the first dose on IELT and increased ejaculatory control, decreased distress, and increased satisfaction. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE (11). Treatment-related side-effects were dose-dependent and included nausea, diarrhoea, headache and dizziness. Side-effects were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects (12). There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation (13).

Regarding a combination of PDE5 inhibitors with dapoxetine, the addition of dapoxetine to a given regimen of PDE5I inhibitor may increase the risk of possible prodromal symptoms that may progress to syncope compared to both PDE5I inhibitors and SSRIs administered alone. Generally, when dapoxetine is co-administered with a PDE5I inhibitor, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone (14). A low rate of vasovagal syncope was reported in phase 3 studies. According to the summary of product characteristics, orthostatic vital signs (blood pressure and heart rate) must be measured prior to starting dapoxetine. No cases of syncope were observed in a post-marketing observational study, which had identified patients at risk for orthostatic reaction using the patient's medical history and orthostatic testing (15).

The mechanism of action of short-acting SSRIs in PE is still speculative. Dapoxetine resembles the antidepressant SSRIs in the following ways: the drug binds specifically to the 5-HT reuptake transporter at subnanomolar levels, has only a limited affinity for 5-HT receptors and is a weak antagonist of the 1A-adrenoceptors, dopamine D1 and 5-HT2B receptors. The rapid absorption of dapoxetine might lead to an abrupt increase in extracellular 5HT following administration that might be sufficient to overwhelm the compensating autoregulation processes. Does the mechanism of action of short-acting SSRIs differ from that of the conventional chronic SSRI mechanism of action? Either such agents do not cause the autoreceptor activation and compensation reported using chronic SSRIs, or these effects occur but they simply cannot prevent the action of short-acting SSRIs (16).

4.8.2.1 Guideline recommendation

On-demand treatment of PE	LE	GR
Dapoxetine on demand	1a	A

*4.8.3 **Off-label use of antidepressants: SSRIs and clomipramine***

Ejaculation is commanded by a spinal ejaculation generator (17,18) under excitatory or inhibitory influences from the brain and the periphery (19). 5-hydroxytryptamine (5-HT or serotonin) is involved in ejaculatory control, with its ejaculation-retarding effects likely to be attributable to activation of 5-HT1B and 5-HT2C receptors, both spinally and supraspinally. By contrast, stimulation of 5-HT1A receptors precipitates ejaculation (20).

Selective serotonin reuptake inhibitors (SSRIs) are used to treat mood disorders, but can delay ejaculation and are therefore widely used 'off-label' for PE. As for depression, SSRIs must be given for 1 to 2 weeks to be effective in PE (20). Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitizes the 5-HT1A and 5-HT1B receptors (21). Clomipramine, the most serotoninergic tricyclic antidepressant, was first reported in 1973 as an effective PE treatment (22). SSRIs have revolutionized treatment of PE, but they have also changed our understanding of PE since the first publication on paroxetine in 1970 (23). Before dapoxetine, daily treatment with SSRIs was the first choice of treatment in PE. Commonly used SSRIs include citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have a similar pharmacological mechanism of action.

A systematic review and meta-analysis of all drug treatment studies reported that, despite methodological problems in most studies, there still remained several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE (24). Open-design studies and those using subjective reporting or questionnaires showed greater variation in ejaculation delay than double-blind studies in which the ejaculation delay was prospectively assessed with a stopwatch.

Based on this meta-analysis, SSRIs were expected to increase the geometric mean IELT by 2.6-fold to 13.2-fold. Paroxetine was found to be superior to fluoxetine, clomipramine and sertraline. Sertraline was superior to fluoxetine, whereas the efficacy of clomipramine was not significantly different from fluoxetine and sertraline. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, fluoxetine 10-60 mg and clomipramine 25-50 mg; there was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective (25,26).

Ejaculation delay may start a few days after drug intake, but it is more evident after 1 to 2 weeks since receptor desensitization requires time to occur. Although efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after 6 to 12 months (22). Common side-effects of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration; they are usually mild and gradually improve after 2 to 3 weeks (22). Decreased libido, anorgasmia, anejaculation and ED have been also reported.

Because of a theoretical risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents with PE aged 18 years or less, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily dosed SSRIs which may be associated with a SSRI withdrawal syndrome (12).

In one controlled trial, on-demand use of clomipramine (but not paroxetine), 3 to 5 hours before intercourse, was reported to be efficacious, though IELT improvement was inferior compared to daily treatment with the same drug (27). However, on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects (28,29).

Individual countries' regulatory authorities strongly advise against prescribing medication for indications if the medication in question is not licensed/approved and prescription of off-label medication may present difficulties for physicians.

4.8.3.1 Guideline recommendation

Chronic treatment of PE	**LE**	**GR**
Off-label chronic treatment i.e. daily with selective serotonin receptor inhibitors (SSRIs) and clomipramine antidepressants	1a	A

*4.8.4 **Topical anaesthetic agents***

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE (30). Several trials (31,32) support the hypothesis that topical desensitizing agents reduce the sensitivity of the glans penis so delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation.

4.8.4.1 Lidocaine-prilocaine cream

In a randomized, double-blind, placebo-controlled trial, lidocaine-prilocaine cream increased the IELT from 1 minute in the placebo group to 6.7 minutes in the treatment group (33). In another randomized, double-blind, placebo-controlled trial, lidocaine-prilocaine cream significantly increased the stopwatch-measured IELT from

1.49 to 8.45 minutes while no difference was recorded in the placebo group (1.67 to 1.95 minutes) (34).

Lidocaine-prilocaine cream (5%) is applied for 20-30 minutes prior to intercourse. Prolonged application of topical anaesthetic (30-45 minutes) may result in loss of erection due to numbness of the penis in a significant percentage of men (33). A condom will prevent diffusion of the topical anaesthetic agent into the vaginal wall causing numbness in the partner.

Alternatively, the condom may be removed prior to sexual intercourse and the penis washed clean of any residual active compound. Although no significant side-effects have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any part of the product.

An experimental aerosol formulation of lidocaine, 7.5 mg, plus prilocaine, 2.5 mg (Topical Eutectic Mixture for Premature Ejaculation [TEMPE]), was applied 5 minutes before sexual intercourse in 539 males. There was an increase in the geometric mean IELT from a baseline of 0.58 minutes to 3.17 minutes during 3 months of double-blind treatment; a 3.3-fold delay in ejaculation compared with placebo ($p < 0.001$) (35).

4.8.4.2 Guideline recommendation

On-demand topical therapy for PE	**LE**	**GR**
Lidocaine-prilocaine cream	1b	A

*4.8.5 **Tramadol***

Tramadol is a centrally acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline. Tramadol is readily absorbed after oral administration and has an elimination half-life of 5-7 hours. For analgesic purposes, tramadol can be administered between 3 and 4 times daily in tablets of 50-100 mg. Side-effects were reported at doses used for analgesic purposes (up to 400 mg daily) and include constipation, sedation and dry mouth. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT (36). This mechanism of action distinguishes tramadol from other opioids, including morphine. However, in May 2009, the US Food and Drug Administration released a warning letter about tramadol's potential to cause addiction and difficulty in breathing (37).

One placebo-controlled study reported that tramadol HCl significantly increased IELT compared with placebo (38). A larger, randomized, double-blind, placebo-controlled, multicentre 12-week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by orally disintegrating tablet (ODT) in the treatment of PE (39). Previously, a bioequivalence study had previously been performed that demonstrated equivalence between tramadol ODT and tramadol HCl. In patients with a history of lifelong PE and an IELT < 2 minutes, increases in the median IELT of 0.6 minutes (1.6-fold), 1.2 minutes (2.4-fold) and 1.5 minutes (2.5-fold) were reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively. It should be noted that there was no dose-response effect with tramadol. The tolerability during the 12-week study period was acceptable.

Overall, tramadol has shown a moderate beneficial effect with a similar efficacy as dapoxetine. From what is known about the neuropharmacology of ejaculation and the mechanism of action of tramadol, the delaying effect on ejaculation could be explained by combined CNS μ-opioid receptor stimulation and increased brain 5-HT availability. However, the beneficial effect of tramadol in PE is yet not supported by a high level of evidence. In addition, efficacy and tolerability of tramadol would have to be confirmed in more patients and longer term.

4.8.5.1 Guideline recommendation

On-demand treatment of PE	**LE**	**GR**
Tramadol on demand	2a	B

*4.8.6 **Other drugs***

4.8.6.1 Phosphodiesterase type 5 inhibitors

There is only one well-designed, randomized, double-blind, placebo-controlled study comparing sildenafil to placebo (40). Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and decreased the refractory time to achieve a second erection after ejaculation.

Several open-label studies showed that sildenafil combined with an SSRI is superior to SSRI monotherapy:

- Sildenafil combined with paroxetine improved IELT significantly and satisfaction versus paroxetine alone (41).
- Sildenafil combined with sertraline improved IELT and satisfaction significantly versus sertraline alone (42).
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed (43).
- Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction versus behavioural therapy alone (44).

There is limited data in PE on the efficacy of other PDE5Is (tadalafil and vardenafil) (45,46). Overall, the role of PDE5Is in PE patients without ED is not established, with only minimal double-blind placebo controlled data available.

4.8.6.2 Guideline recommendation

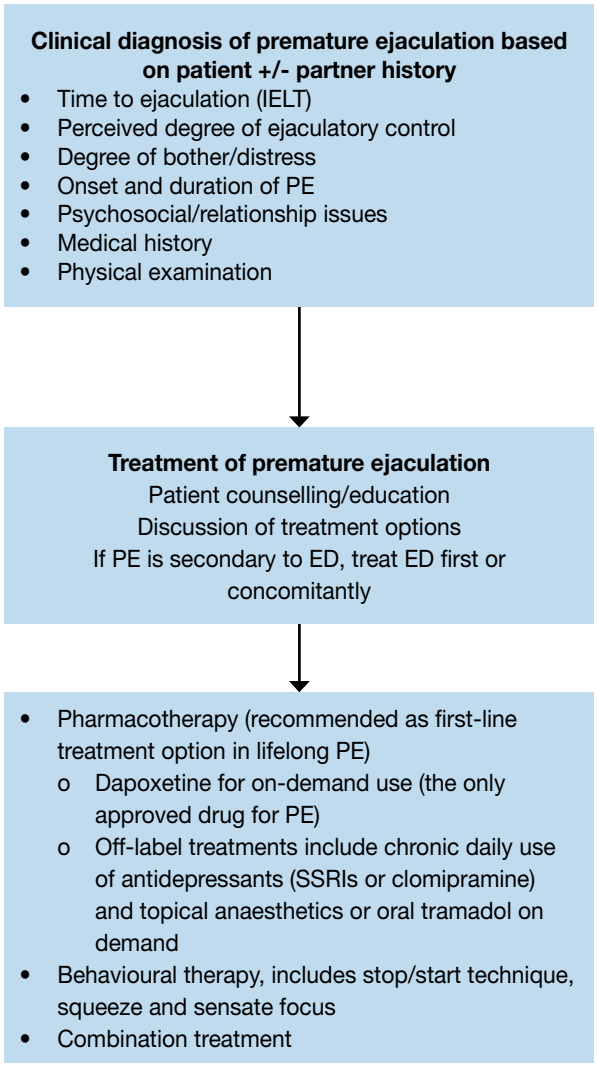
On-demand treatment of PE	**LE**	**GR**
PDE5 inhibitors	3	C

*4.8.7 **Guidelines on treatment of PE***

Recommendations	**LE**	**GR**
Erectile dysfunction, other sexual dysfunction or genitourinary infection (e.g. prostatitis) should be treated first.	2a	B
Pharmacotherapy should be given as first-line treatment of lifelong PE.	1a	A
Pharmacotherapy includes either dapoxetine on demand (a short-acting SSRI that is the only approved pharmacological treatment for PE) or other off-label antidepressants, i.e. daily SSRIs and clomipramine, that are not amenable to on-demand dosing. With all antidepressant treatment for ED, recurrence is likely after treatment cessation.	1a	A
Off-label topical anaesthetic agents can be offered as a viable alternative to oral treatment with SSRIs.	1b	A
Behavioural and sexological therapies have a role in the management of acquired PE. They are most likely to be best used in combination with pharmacological treatment.	3	C

ED = erectile dysfunction; PE = premature ejaculation; SSRI = selective serotonin reuptake inhibitor.

Figure 4: Management of PE*



* Adapted from Lue et al. 2004 (47).
ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

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5. CONCLUSION

Modern treatment of ED has been revolutionized by the worldwide availability of three PDE5Is for oral use: sildenafil, tadalafil and vardenafil. These drugs have high efficacy and safety rates, even in difficult-to-treat populations, such as patients with diabetes mellitus or who have undergone radical prostatectomy. Patients should be encouraged to try all three PDE5Is. Patients should make up their own minds about which compound has the best efficacy, while also considering other factors, such as time of onset, duration of action, window of opportunity and how side-effects affect them individually.

Treatment options for patients who do not respond to oral drugs, or for whom drugs are contraindicated, include intracavernous injections, vacuum constriction devices, or implantation of a penile prosthesis as a last option.

It is very important that the physician warns the patient that sexual intercourse is a vigorous physical activity, which increases heart rate and cardiac work. Physicians should assess a patient's cardiac fitness prior to treating ED.

Any successful pharmacological treatment for erectile failure demands a degree of integrity of the penile mechanisms of erection. Further studies of individual agents and synergistic activity of available substances are underway. The search for the ideal pharmacological therapy for erectile failure aims to fulfil the following characteristics: good efficacy, easy administration, freedom from toxicity and side-effects, with a rapid onset and a possible long-acting effect.

Premature ejaculation is another very common male sexual dysfunction. Four major definitions of PE are currently used and the most widely accepted classification of PE includes 'lifelong' (primary) and 'acquired' (secondary) forms (syndromes).

Diagnosis of PE in everyday clinical practice is based on medical and sexual history assessing IELT, perceived control, distress, and interpersonal difficulty related to the ejaculatory dysfunction. A targeted physical examination is advisable but not mandatory.

Pharmacotherapy is the basis of treatment in lifelong PE, including dapoxetine on demand, the only approved drug for the treatment of PE, off-label daily dosing of SSRIs and clomipramine and topical anaesthetics. Behavioural techniques may be efficacious as a monotherapy or in combination with pharmacotherapy, but they can be difficult to perform. In every case, recurrence is likely to occur after treatment withdrawal.

6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

5-HT	5-hydroxytryptamine
AIPE	Arabic Index of Premature Ejaculation
AUC	area under curve (serum concentration time curve)
BMI	body mass index
CAD	coronary artery disease
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CHF	congestive heart failure
Cmax	maximal concentration
DICC	dynamic infusion cavernosometry or cavernosography
DRE	digital rectal examination
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision
EAU	European Association of Urology
ED	erectile dysfunction
EMEA	European Medicines Agency
FDA	(US) Food and Drug Administration
FSH	follicle-stimulating hormone
GAQ	General Assessment Question
GR	grade of recommendation
GSSAB	Global Study of Sexual Attitudes and Behaviors
ICD-10	International Classification of Diseases-10
IELT	intravaginal ejaculatory latency time
IIEF	International Index for Erectile Function
IIEF-EF	International Index for Erectile Function - erectile function domain
IPE	Index of Premature Ejaculation
ISSM	International Society for Sexual Medicine
LE	level of evidence
LH	luteinizing hormone
LVD	left ventricular dysfunction
MET	metabolic equivalent of energy expenditure in the resting state
MI	myocardial infarction
MMAS	Massachusetts Male Aging Study
MSHQ-EjD	Male Sexual Health Questionnaire Ejaculatory Dysfunction
NHSLS	National Health and Social Life Survey
NS	nerve sparing
NO	nitric oxide
NPTR	nocturnal penile tumescence and rigidity
NSRP	nerve-sparing radical prostatectomy
NYHA	New York Heart Association
PCa	prostate cancer
PDE5[I]	phosphodiesterase type 5 [inhibitors]
PE	premature ejaculation
PEDT	Premature Ejaculation Diagnostic Tool
PEP	Premature Ejaculation Profile
PEPA	Premature Ejaculation Prevalence and Attitudes
PRO	Patient reported outcome
PSA	prostate-specific antigen
QoL	quality of life
RP	radical prostatectomy
SEP	sexual encounter profile
SSRI	selective serotonin reuptake inhibitor
TEMPE	topical eutectic mixture for premature ejaculation
Tmax	time to maximum plasma concentration
VCD	vacuum constriction devices
VIP	vasointestinal peptide

Conflict of interest

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